THE CARLAT REPORT PSYCHIATRY

A CME Publication

Subscribe today! Call 866-348-9279

AN UNBIASED MONTHLY COVERING ALL THINGS PSYCHIATRIC

Chris Aiken, MD
Editor-in-Chief

Volume 22, Issue 1
January 2024
www.thecarlatreport.com

IN THIS ISSUE

Focus of the Month: **Depression**

Zuranolone for Postpartum Depression — 1

Expert Q&A: — 1
How to Choose an Antidepressant
Thomas Schwartz, MD

Negative Symptoms of Schizophrenia — 5

Table: Negative Symptoms of Schizophrenia: Treatment Guide — 5

Research Update: — 6
- Perinatal Bipolar Mood Episodes: More Prevalent Than We Thought

CME Test — 7

Learning Objectives

After reading these articles, you should be able to:

1. Understand how to use zuranolone for postpartum depression and its potential efficacy in major depression.
2. Identify appropriate first-line antidepressant choices based on patient-specific factors such as side effects, age, and medical considerations.
3. Identify potential treatments for negative symptoms in schizophrenia.
4. Summarize some of the current research findings on psychiatric treatment.

Zuranolone for Postpartum Depression

Chris Aiken, MD. Editor-in-Chief, The Carlat Psychiatry Report. *Assistant Professor, NYU Langone Department of Psychiatry. Practicing psychiatrist, Winston-Salem, NC.*

Dr. Aiken has no financial relationships with companies related to this material.

On August 4, 2023, the FDA approved zuranolone (Zurzuvae, "zur-ZOO-vay") for postpartum depression (PPD). The medication is an oral version of IV brexanolone (Zulresso), which was approved for the same indication in 2019. Brexanolone stalled, with just over 1,000 women receiving it, because of its high cost and requirement for overnight monitoring. Both drugs bring a novel mechanism to the table, and in this article I'll look at what that means for depression in postpartum and beyond.

Rapid action

Zuranolone works quickly. It is given as a two-week course, and the benefits are seen within three days. This kind of rapid onset is particularly important in PPD, where every day of active symptoms takes a measurable toll on infant development.

Continued on page 2

Highlights From This Issue

Feature article. Zuranolone brings rapid relief in postpartum depression, but is it any different from a benzo?

Q&A. Dr. Thomas Schwartz explains the art of matching patients with antidepressants, and finds these underutilized: levomilnacipran, trazodone, and vilazodone.

Article on page 5. For antipsychotics that reduce negative symptoms, cariprazine and clozapine come first, followed by amisulpride, olanzapine, asenapine, and perphenazine.

Q&A With the Expert

How to Choose an Antidepressant
Thomas Schwartz, MD

Professor and Chair, Department of Psychiatry and Behavioral Sciences, Alan and Marlene Norton College of Medicine, SUNY Upstate Medical University, Syracuse, NY.

Dr. Schwartz has no financial relationships with companies related to this material.

TCPR: How do you choose a first-line antidepressant in major depression?

Dr. Schwartz: There are about 30 antidepressants, and they all have moderate benefits. To start, pick one that's low risk—not a tricyclic, where there are cardiac problems and overdose fatalities to worry about, and not an MAOI, where people can die from strokes or heart attacks if they eat a tyramine-rich meal or mix the MAOI with a medication that causes serotonin syndrome. Tricyclics and MAOIs can be very effective, so I might use them if there's no response to a first-line agent, but I'll start with something safer—in other words, most of the antidepressants released since the 1980s.

TCPR: How do you divide those up?

Dr. Schwartz: I divide the antidepressants into roughly four categories. First, we have selective serotonin reuptake inhibitors (SSRIs),

Continued on page 3

Zuranolone for Postpartum Depression

Continued from page 1

On the other hand, we don't know how long those benefits will last. Zuranolone's approval was based on two randomized trials that followed patients for four weeks after their last dose. No decline was seen at that point, but this was a select group where active psychosis, suicidality, and bipolar were excluded.

Mailing Information

The Carlat Psychiatry Report (ISSN 2473-4128) is published monthly, excluding July and Nov., by Carlat Publishing, LLC; 2 Prince Place, Newburyport, MA 01950. Periodicals Postage Paid at Newburyport, MA and at additional mailing offices.

POSTMASTER: Send address changes to *The Carlat Psychiatry Report*, P.O. Box 626, Newburyport, MA 01950.

In practice, patients with PPD often have more complex histories and high levels of recurrence. In these trials, 89% were in their first postpartum episode (Deligiannidis KM et al, *JAMA Psychiatry* 2021;78(9):951–959; Deligiannidis KM et al, *Am J Psychiatry* 2023;180(9):668–675).

Non-postpartum depression

While both postpartum trials were positive with a respectable effect size (0.5), zuranolone's course in general depression has been uneven. The manufacturer, Sage Therapeutics, first tested it in treatment-resistant depression. Failing there, they moved on to major depressive disorder (MDD) and found success in a small controlled trial. However, the large, follow-up MOUNTAIN study was negative, prompting the company to try again at a higher dose of 50 mg instead of 20–30 mg (Clayton AH et al, *J Clin Psychiatry* 2023;84(2):22m14445).

What followed were two large controlled trials that are often presented as positive but did not convince the FDA. Zuranolone surpassed placebo, but only for a few days. Over the two-week course of treatment, it fizzled out before the treatment was over in the CORAL study and just after the final dose in the WATERFALL study (Carvalho T, *Nat Med* 2023;29(5):1032–1033). Zuranolone's mechanism of action may explain these conflicting results.

How it works

Like the benzodiazepines, zuranolone is a positive allosteric modulator of the GABA-A receptor. Unlike the benzodiazepines, it binds to a different area of GABA-A, upregulates the receptor, and has broader effects on GABAergic transmission (Stahl S et al, *CNS Spectr* 2023;28(2):260–261).

These actions mimic the effects of allopregnanolone, a hormone that rises during pregnancy and falls after delivery. The sudden fall in allopregnanolone contributes to the pathophysiology of PPD. Brexanolone (approved as an IV treatment for PPD) is chemically identical to allopregnanolone, and zuranolone is a slightly modified version designed to enhance oral absorption. In theory, they treat PPD by easing allopregnanolone withdrawal.

No such elegant mechanism exists for zuranolone in MDD. Until proven otherwise, it's hard to see how this drug is any different in MDD from a benzodiazepine.

Besides sharing a common mechanism with the benzos, zuranolone shares in their anxiolytic, hypnotic, and rewarding effects. One study asked subjects with a history of sedative misuse to compare zuranolone, alprazolam, and placebo. Zuranolone made them feel euphoric and drunk, and they found it just as rewarding as alprazolam, according to FDA data cited in *PDR*.

It is not surprising that a medication with benzo-like properties would improve depression, if only temporarily. Benzodiazepines have robust short-term data in MDD, particularly alprazolam, which earned an initial FDA approval in MDD (van Marwijk H et al, *Cochrane Database Syst Rev* 2012;2012(7):CD007139). That approval was downgraded to "anxiety associated with depression" upon alprazolam's release in 1981, in part due to concerns about tolerance and drug misuse.

Because of these similarities, zuranolone is classified along with the benzodiazepines as a Schedule IV controlled drug, as is its IV cousin brexanolone.

Bipolar disorder, psychosis, and suicide

While zuranolone is praised as a breakthrough for PPD, we have to acknowledge that the most severe forms of this disorder were excluded from the trials: bipolar depression, psychotic depression, and patients with an elevated suicide risk.

PPD is more common in bipolar disorder, and postpartum episodes should raise suspicion for bipolarity. Whether zuranolone will work in these cases is unknown, but there was no sign of manic switching in the depression trials. Studies are underway in bipolar depression, and so far they have produced a small open-label trial where 45% of the subjects responded to a two-week course of zuranolone (Meshkat S et al, *J Affect Disord* 2023;S0165-0327(23)01003-0).

Side effects and drug interactions

Zuranolone's main side effects are drowsiness, dizziness, and diarrhea. One in four women experienced significant fatigue, although unlike brexanolone, it did not

Continued on page 3

Zuranolone for Postpartum Depression

Continued from page 2

cause loss of consciousness. Zuranolone can impair driving for up to 12 hours after the dose. It is not recommended in breastfeeding because its safety is untested. Women who intend to breastfeed should pump during the treatment in order to maintain their lactation ability.

Zuranolone is vulnerable to drug interactions at CYP3A4. Patients will need a higher dose to adjust for CYP3A4 inducers (eg, carbamazepine and the modafinils) and a lower dose for CYP3A4 inhibitors (eg, nefazodone, fluvoxamine, and grapefruit juice). Otherwise, it can be taken with other antidepressants, as it was for one in five women in the trials. However, other GABAergics like benzos, z-hypnotics, and alcohol were not allowed in the trials, so use caution until we have more clarity on those interactions.

How to use it

Zuranolone is dosed once at night for two weeks. It needs to be taken with a high-fat meal of at least 400 calories in order to be absorbed. The starting and treating dose is 50 mg, and this can be lowered if it causes problematic side effects like fatigue. The two postpartum trials found similar benefits with the 30 and 50 mg doses.

The FDA has not addressed the issue of repeated trials, but this strategy was tested in a large open-label study of MDD. In the year following treatment, 55% of patients required a second two-week course of zuranolone, and 16% required three or four additional courses (Meshkat et al, 2023).

CARLAT VERDICT

Zuranolone brings rapid relief to PPD. It is taken over two weeks, and its benefits last at least a month. In major depression, its role is less clear, and we have yet to see evidence that it is any better than a benzodiazepine there.

Expert Interview

Continued from page 1

such as fluoxetine and sertraline. Next are serotonin-norepinephrine reuptake inhibitors (SNRIs), like venlafaxine and duloxetine. Third are serotonin antagonist reuptake inhibitors (SARIs), like trazodone and nefazodone, which are sedating. Fourth are norepinephrine-dopamine reuptake inhibitors (NDRIs), like bupropion, which are more activating.

TCPR: What about the newest editions: vortioxetine (Trintellix) and vilazodone (Viibryd)?

Dr. Schwartz: I'd classify them as serotonin partial agonist reuptake inhibitors (SPARIs). Like the SSRIs, they manipulate the serotonin receptors, but they do a little more. I should add that mirtazapine often gets lumped with the sedating antidepressants, but it's really in a class of its own. It's a serotonin receptor antagonist at a couple of places, and it enhances norepinephrine by blocking an alpha-2 receptor.

TCPR: I've counted 15 post-1980 antidepressants with six receptor profiles. How do you choose among them?

Dr. Schwartz: It comes down to the patient in front of you, and side effects are usually going to guide the choice. Most people start with an SSRI, but some patients just don't tolerate these or the closely related SNRIs. At first patients experience headache and GI distress, but that is usually manageable by slowing the titration. Over the long term they experience sexual dysfunction and weight gain, which can be a deal-breaker. Another deal-breaker is when patients feel tired or wired on SSRIs and SNRIs.

TCPR: What does "wired" look like?

Dr. Schwartz: Agitated, anxious, and restless. You can even see overt akathisia; it is rare but possible (Koliscak LP and Makela EH, *J Am Pharm Assoc* 2009;49(2):e28–e38). Like other antidepressants, SSRIs can induce mania, which creates hyperactivity as well.

TCPR: What can you use instead?

Dr. Schwartz: Before starting an antidepressant, I'll want to know if the patient is very fatigued, or if they are agitated and can't sleep. If they are fatigued, I'll lean toward an activating agent like the NDRI bupropion. I may also prefer bupropion if weight gain or sexual side effects are a problem, although vortioxetine, trazodone, and mirtazapine also have low rates of sexual side effects. If they are agitated, I'll prefer a sedating agent like trazodone or mirtazapine.

TCPR: How do SSRIs affect sleep quality?

Dr. Schwartz: SSRIs and SNRIs can disrupt sleep quality, but trazodone and mirtazapine usually improve it, possibly because they block serotonin-2A receptors (Gulec M et al, *J Affect Disord* 2011;134(1–3):257–265). Patients don't sleep with an EEG on, so you have to look to other signs to pick up on this. They'll say, "My depression didn't make me tired before, but I'm tired now," "I feel fuzzy and unfocused," or, "I wake up six or seven times throughout the night." It helps to catalog these symptoms before you start an antidepressant. Otherwise, you can end up causing side effects that look like untreated depressive symptoms.

TCPR: You mentioned weight gain. Which antidepressants are more favorable there?

Dr. Schwartz: Bupropion. It tends to suppress appetite, and I rarely if ever see weight gain on it. Mirtazapine is probably the worst, but the other sedating antidepressants—nefazodone and trazodone—are more favorable when it comes to weight (Gill H et al, *Obesity* 2020;28(11):2064–2072). On average, weight gain is mild with SSRIs and SNRIs, but some people gain a lot on them, like 20–30 pounds over several years. Serotonin affects hormones involved in weight, like leptin, and may cause fat cells to grow. My guess is that some people's genes don't match well with that. However, the SPARIs (vortioxetine and vilazodone) seem to have an advantage here, even though they are serotonergic.

TCPR: Which antidepressants have lower rates of sexual side effects?

Dr. Schwartz: Bupropion tops that list again, but we can also add the sedating antidepressants: nefazodone, trazodone, and mirtazapine. The SPARIs (vortioxetine and vilazodone) also seem to spare the sex drive, particularly vilazodone (Reichenpfader U et al, *Drug Saf* 2014;37(1):19–31).

Continued on page 4

Expert Interview
Continued from page 3

TCPR: Do any antidepressants stand out for cognitive benefits?

Dr. Schwartz: Bupropion might help cognition. It has positive trials in ADHD and in depression, but the depression studies were not randomized (Gualtieri CT and Johnson LG, *MedGenMed* 2007;9(1):22). Bupropion affects norepinephrine and dopamine, which in theory are the monoamines that are most likely to improve cognition. The sedating antidepressants can go both ways. If they improve sleep quality, the patient may be a little sharper, but if they cause too much sedation they could make things worse. Then there's vortioxetine, which tried but failed to earn FDA approval for cognitive symptoms of depression. The problem was that its benefits were not broad enough. It only changed one measure of cognition, the digit symbol substitution test, which is a measure of attention and processing speed (Huang IC et al, *Int J Neuropsychopharmacol* 2022;25(12):969–978).

TCPR: Bupropion was released before the SSRIs, but the SSRIs have always been more popular. Why is that?

Dr. Schwartz: Bupropion got off to a bad start because it was pulled from the shelves for causing seizures shortly after its release. They reintroduced it a few years later with safer dosing guidelines—we don't go beyond 450 mg/day anymore—and the extended-release forms have made it safer still (Steinert T and Fröscher W, *Pharmacopsychiatry* 2018;51(4):121–135). But by the time of the reintroduction, fluoxetine (Prozac) had already hit the market, and it came with an advertising blitz that bupropion never caught up with.

TCPR: Does the patient's age influence the choice of antidepressant?

Dr. Schwartz: Fluoxetine and escitalopram are usually first line if the patient is under age 18, as these are the only two with FDA approval in that age group. Many others tried but did not succeed. I'm also comfortable with sertraline and duloxetine, which are FDA approved in childhood OCD (sertraline) and generalized anxiety disorder (duloxetine). That reassures me of their relative safety in younger patients. If these don't work, you're dealing with treatment-resistant depression (TRD) and need to move up to the adult guidelines for TRD as we don't have many data in children (Dwyer JB and Bloch MH, *Curr Psychiatr* 2019;18(9):26–42F).

"In choosing an antidepressant, it comes down to the patient in front of you, and side effects are usually going to guide the choice."

Thomas Schwartz, MD

TCPR: What about older adults?

Dr. Schwartz: For elderly folks, I start with one of the post-1980 antidepressants we just reviewed and personalize based on their symptoms and side effects, just as I'd do for general adults. The only difference is that I'll start low and go slow, but I'll still aim for the full dose range. Also, I'll think more about drug interactions in older adults. Among the serotonergics, desvenlafaxine, escitalopram, and sertraline (at doses below 150 mg) have the lowest risk of drug interactions. Citalopram has a warning about QT prolongation in the elderly, so I try to avoid that one.

TCPR: Some antidepressants are more prone to withdrawal problems. How does that influence your decision?

Dr. Schwartz: Most antidepressants are associated with withdrawal phenomena, but it's worse with the SSRIs and SNRIs, particularly the short half-life drugs: desvenlafaxine, duloxetine, venlafaxine, and paroxetine (Horowitz MA et al, *CNS Drugs* 2023;37(2):143–157). It's not a lethal problem, but it is very unpleasant (like you have the flu), and these withdrawal problems are worse the longer they've been on the med. It's less of an issue with a drug like fluoxetine, which has a long half-life and thus may be better suited for patients who tend to miss their dose here and there.

TCPR: What about melancholic depression? I'm thinking about patients with early-morning awakening, worse mood in morning, low appetite, ruminative guilt, and significant psychomotor slowing or agitation. Do you prefer any antidepressants there?

Dr. Schwartz: The FDA doesn't evaluate that subtype, but if we look outside the FDA data, I think it favors the tricyclics. If the patient can't tolerate a tricyclic, I would go with an SNRI, which is the closest thing to a tricyclic.

TCPR: How do you choose among the SNRIs?

Dr. Schwartz: One way they differ is in their medical risks. With duloxetine, we worry about liver toxicity, so I'm likely to avoid that in someone who drinks a lot of alcohol or takes other meds like statins that can impair the liver (Todorović Vukotić N et al, *Arch Toxicol* 2021;95(3):767–789). On the other hand, duloxetine is the only SNRI that doesn't carry a warning about raising blood pressure. Duloxetine would be a good choice for a patient with urinary incontinence (it has regulatory approval for that in other countries), but this mechanism also means it can cause urine retention in vulnerable patients. Overall, for medically compromised patients I prefer desvenlafaxine. It is the safest on the liver, and it's less affected by drug interactions because it's metabolized outside the P450 system through glucuronidation.

TCPR: What about venlafaxine (Effexor) and levomilnacipran (Fetzima)?

Dr. Schwartz: Venlafaxine stands out for its withdrawal problems. Levomilnacipran doesn't get used much, but I think it does have a niche. It is the most noradrenergic of the SNRIs, much as protriptyline is the more noradrenergic of the tricyclics. It handles a lot like bupropion, and like bupropion it can make people shaky, jittery, as well as sweaty. It's a hard drug to tolerate, so I think you have to titrate it carefully. It's a good option for people who are slowed down and tired. Levomilnacipran is an isomer of milnacipran, which is approved in the US for fibromyalgia (milnacipran is approved for depression in other countries).

TCPR: How do you pick and choose among the SSRIs?

Dr. Schwartz: My impression is that the SSRIs are similar in terms of response. The SNRIs are more unique, so I'm more likely to switch around in that class. If one doesn't work, I will usually move on. In terms of choosing

Continued on page 8

Negative Symptoms of Schizophrenia

Chris Aiken, MD. Editor-in-Chief, The Carlat Psychiatry Report. *Assistant Professor, NYU Langone Department of Psychiatry. Practicing psychiatrist, Winston-Salem, NC.*

Paul Riordan, MD. Assistant Consulting Professor of Psychiatry, Duke University, Durham, NC.

The authors have no financial relationships with companies related to this material.

A 56-year-old man with schizophrenia presents for possible depression, but on closer examination has prominent negative symptoms of schizophrenia. When asked about his relationships, he says he keeps to himself and has no friends (asociality). He spends most of the day in a recliner and has trouble starting simple activities (avolition). He speaks in short, five-word sentences (alogia). Although his brother died recently, he speaks of the loss with minimal facial expressions, matching his monotonic voice (blunted affect). He does, however, enjoy documentaries on the "mysteries of the pyramids," so he lacks the negative symptom of anhedonia.

Negative symptoms like these are part of the core criteria of schizophrenia and are the main cause of disability in this illness. Many treatments have the potential to help, and in this article, we'll highlight the ones that are ready for practice.

Differential diagnosis

The first step is to rule out a variety of other potential causes of negative symptoms.

Is psychosis the cause?

Symptoms that appear to be negative symptoms can be due to the psychosis itself. In the case above, if the patient heard voices telling him not to leave his recliner, we'd start by treating the active psychosis.

Comorbid conditions

Next, address comorbidities that might be contributing to the picture, like depression, PTSD, substance use, insomnia, and sleep apnea.

Antipsychotic side effects

Antipsychotic side effects can resemble negative symptoms, such as sedation, muscle stiffness, parkinsonian slowing, and amotivation.

Antipsychotics

It is difficult to know for sure whether antipsychotics directly improve negative symptoms, versus improving them only indirectly through treatment of active psychosis. We need trials that test antipsychotics in patients who have recovered from psychosis but continue to experience prominent negative symptoms, and so far we have only a few.

One study compared risperidone to cariprazine in patients who continued to have negative symptoms after recovering from a psychotic episode. The results favored cariprazine, though the benefit was small, with a number needed to treat of 9 (Németh G et al, *Lancet* 2017;389(10074):1103–1113). Another large trial found favorable results with amisulpride, a European antipsychotic that may come to the US market in the next few years (Krause M et al, *Eur Arch Psychiatry Clin Neurosci* 2018;268(7):625–639).

Another possibility is clozapine. Although its effects on negative symptoms are not well researched, this medication does bring about higher rates of functional recovery (Kim S et al, *Psychiatry Investig* 2021;18(10):968–976). Compared to other antipsychotics, clozapine had the largest effect size (0.6) for reducing negative symptoms when used during active psychosis, according to a meta-analysis (Huhn M et al, *Lancet* 2019;394(10202):939–951). Next in line after clozapine were amisulpride, olanzapine, asenapine, and perphenazine.

Augmentation

Another option is to augment the antipsychotic, and an antidepressant is a reasonable place to start. Studies of SSRIs have been generally positive, though the benefits are small. On the other hand, duloxetine (Cymbalta), mirtazapine (Remeron), and vortioxetine (Trintellix) have yielded larger effect sizes for negative symptoms, although the studies supporting them are still small in size and few in number (Moazen-Zadeh E et al, *J Psychopharmacol* 2020;34(5):506–513).

Other augmentation options with positive controlled trials are listed in the table "Negative Symptoms of Schizophrenia: Treatment Guide." None stand out as more effective, and all are hindered by small effect sizes (0.2–0.3) and small trials. They include simvastatin, minocycline, 5-HT3 inhibitors (ondansetron, granisetron, tropisetron), lamotrigine, and topiramate, as well as augmentation with the novel

Continued on page 6

Negative Symptoms of Schizophrenia: Treatment Guide

Treatment	Daily Dose	Notes
Clozapine	100–900 mg	Large effect size (0.6), efficacy in treatment-resistant patients
Curcumin	3000 mg	Brands with bioperine are better absorbed
Duloxetine	30–60 mg	Raises some antipsychotic levels through CYP2D6 interactions
Mirtazapine	30 mg	Risk of weight gain
Ondansetron	8 mg	QT prolongation
Pimavanserin	20–34 mg	Minimal data, low effect size (0.21–0.34), high cost
Sarcosine	2000 mg	Reports of hypomania
Simvastatin	40 mg	Reserve for comorbid dyslipidemia
SSRIs	Citalopram (20–40 mg), escitalopram (10–20 mg), fluoxetine (20–40 mg), fluvoxamine (100–150 mg), sertraline (50–100 mg)	Fluoxetine and fluvoxamine raise some antipsychotic levels
Topiramate	125–175 mg	Cognitive side effects
Vortioxetine	20 mg	Large effect size, but only one study
Lifestyle	Aerobics (30 min twice a week), yoga or tai chi (60 min twice a week)	
Therapy	Cognitive behavioral therapy, mindfulness, and cognitive remediation	

Research Update IN PSYCHIATRY

BIPOLAR DISORDER

Perinatal Bipolar Mood Episodes: More Prevalent Than We Thought

Jeremy Mills, DNP, PMHNP-BC. Dr. Mills has no financial relationships with companies related to this material.

REVIEW OF: Masters et al, *J Clin Psychiatry* 2022;83(5):21r14045

STUDY TYPE: Systematic review and meta-analysis

The perinatal period is a time of increased risk for exacerbation of bipolar disorder. This new analysis tells us just how high that risk is.

In the first systematic review and meta-analysis of 22 observational studies involving perinatal women, researchers looked at the prevalence of bipolar and bipolar spectrum disorders during pregnancy and postpartum. The total population was stratified into two categories: 1) participants without a known psychiatric history and 2) participants with bipolar disorder or probable bipolar disorder, assessed via a diagnostic interview or a diagnostic tool validated in perinatal populations.

Three studies looked at pregnant women, nine studies looked at postpartum women, and 10 studies looked at both. Less than half of the studies used diagnostic interviews to determine the presence of bipolar disorder, but all the studies at least employed screening tools validated in perinatal populations.

Among 6,325 women with no prior psychiatric diagnosis, about 3% developed bipolar disorder during the perinatal period. Among the 2,814 women already diagnosed with bipolar disorder, 55% had a mood episode during the perinatal period.

Compared to those without a prior bipolar disorder diagnosis, perinatal women who were identified with probable bipolar disorder on a screening test were 6.5 times more likely to experience a depressive episode.

The main limitation was that only 45% of the studies looking at previously undiagnosed women used a structured interview to establish the diagnosis. Fifty-five percent relied on the Mood Disorder Questionnaire to establish the diagnosis.

CARLAT TAKE

When a woman shows signs of depression during or after pregnancy, be proactive about screening for bipolar disorder before initiating antidepressant therapy. One in five of these patients could potentially develop full-blown bipolar disorder. It's worth noting that pregnancy significantly ups the ante for patients with existing bipolar disorder, amplifying the risk of fresh mood episodes by nearly seven times.

❖ ❖ ❖

Negative Symptoms of Schizophrenia

Continued from page 5

antipsychotic pimavanserin (Nuplazid). To choose among them, aim for one that addresses active comorbidities, such as simvastatin for dyslipidemia or ondansetron, which has positive trials in OCD and in binge drinking.

It may be surprising to see topiramate on this list. This anticonvulsant's reputation for impairing cognition has earned it the nickname "Dopamax," but negative symptoms involve more than cognition. Topiramate improved negative and positive symptoms in small trials of treatment-resistant schizophrenia, usually as an add-on to clozapine. Its cognitive side effects are reduced by starting low (25 mg/day) and raising slowly (by 25 mg/week). Patients with comorbid obesity, PTSD, OCD, or alcohol or cocaine use disorders may find additional benefits with topiramate (Correll CU et al, *JAMA Psychiatry* 2017;74(7):675–684).

Supplements

Most supplements have mixed results for negative symptoms, but two with steadier track records are sarcosine and curcumin. Sarcosine is a sweet-tasting amino acid that is sold as a nootropic. It has multiple small trials showing a moderate benefit for negative symptoms (Strzelecki D et al, *Hum Psychopharmacol* 2021;36(3):e27770; Singh S and Singh V, *CNS Drugs* 2011;25(10):859–885). Curcumin is an extract of the turmeric spice that now has two small trials showing benefits (Hosseininasab M et al, *J Clin Psychopharmacol* 2021;41(1):25–30). Curcumin also has positive trials in depression and in cognitive problems due to various causes. Both of these supplements have evidence in primary negative symptoms, and both are well tolerated, although there are reports of hypomania on sarcosine.

Exercise

Exercise improves primary negative symptoms in schizophrenia, but only in studies of aerobic exercise, and the effect size is small at 0.31 (Sabe M et al, *Gen Hosp Psychiatry* 2020;62:13–20). "Aerobic" means any activity that hastens breathing and raises pulse by at least 10 bpm. The minimum dose is 30 minutes twice a week over six months. If aerobic exercise is too strenuous, mind-body exercises like yoga or tai chi for two hours a week may also help (Sabe M et al, *Schizophr Res* 2019;212:15–25). These are challenging prescriptions to follow when a patient suffers from significant amotivation. Recruiting friends or family for dual participation is often necessary.

Psychotherapy

Psychotherapies (specifically cognitive behavioral therapy for psychosis, acceptance and commitment therapy, and metacognitive therapy) show small benefits for primary negative symptoms (Lutgens L et al, *Br J Psychiatry* 2017;210:324–332).

Continued on page 7

CME Post-Test

To earn CME or CE credit, log on to www.TheCarlatReport.com to take the post-test. You will be given two attempts to pass the test. You must answer 75% of the questions correctly to earn credit. Tests must be completed within a year from each issue's publication date. The Carlat CME Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Carlat CME Institute maintains responsibility for this program and its content. Carlat CME Institute designates this enduring material educational activity for a maximum of one (1) *AMA PRA Category 1 Credit*™. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity. This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Learning Objectives are listed on page 1.

1. Why is the rapid onset of zuranolone particularly important in the context of postpartum depression (PPD) (LO #1)?

   [ ] a. The rapid onset allows for better sleep quality
   [ ] b. Quick symptom relief may reduce the toll on the neonate
   [ ] c. Zuranolone directly targets bipolar disorder symptoms
   [ ] d. Zuranolone provides long-lasting relief for PPD

2. According to Dr. Schwartz, which class of antidepressant should be considered for a patient who presents with significant fatigue (LO #2)?

   [ ] a. Selective serotonin reuptake inhibitor
   [ ] b. Tricyclic antidepressant
   [ ] c. Norepinephrine-dopamine reuptake inhibitor
   [ ] d. Serotonin antagonist reuptake inhibitor

3. Which antipsychotic demonstrated positive results on negative symptoms in a study involving patients with schizophrenia who had recovered from a psychotic episode but continued to experience prominent negative symptoms (LO #3)?

   [ ] a. Risperidone [ ] b. Cariprazine [ ] c. Amisulpride [ ] d. Olanzapine

4. According to findings from a 2022 meta-analysis by Masters and colleagues, what is the prevalence of bipolar disorder among perinatal women with no prior psychiatric diagnosis (LO #4)?

   [ ] a. Greater than 12% [ ] b. Approximately 6.5% [ ] c. Approximately 3% [ ] d. Nonexistent

5. Compared to the benzodiazepines, how does zuranolone differ in terms of mechanism of action (LO #1)?

   [ ] a. It doesn't bind to GABA-A receptors
   [ ] b. It primarily affects serotonin receptors
   [ ] c. It has broader effects on GABAergic transmission
   [ ] d. It induces manic switching in patients with depression

6. Which two antidepressants are FDA approved for treating major depression in patients younger than 18 years (LO #2)?

   [ ] a. Citalopram and fluoxetine
   [ ] b. Escitalopram and fluoxetine
   [ ] c. Sertraline and fluoxetine
   [ ] d. Duloxetine and fluoxetine

7. Which exercise regimen has been shown to improve primary negative symptoms in schizophrenia, with a small but measurable effect size (LO #3)?

   [ ] a. Strength training
   [ ] b. Aerobic exercise
   [ ] c. Mind-body exercises
   [ ] d. High-intensity interval training

8. Unlike the benzodiazepines, zuranolone is not classified as a controlled drug (LO #1).

   [ ] a. True [ ] b. False

Negative Symptoms of Schizophrenia

Continued from page 6

Cognitive remediation is an even better treatment option, with the most rigorous trials improving negative symptoms with a medium effect size (Cella M et al, *Clin Psych Rev* 2017;52:43–51). This makes intuitive sense as it focuses directly on improving cognitive functioning.

TMS

Neuromodulation techniques are the latest to show promise in negative symptoms. Repetitive transcranial magnetic stimulation (rTMS) brought improvements in several randomized controlled trials (Tseng PT et al, *JAMA Psychiatry* 2022;79(8):770–779). Insurance is unlikely to cover off-label use of rTMS, and other neuromodulation options with potential benefits (eg, high-definition transcranial random noise stimulation, anodal transcranial direct current stimulation) are not yet clinically available.

CARLAT VERDICT

To treat negative symptoms, start with an antipsychotic that has evidence to help this disabling phase of schizophrenia, particularly cariprazine and possibly olanzapine, asenapine, perphenazine, or—for treatment-resistant cases—clozapine. Next, try augmentation, either with an antidepressant (duloxetine or vortioxetine) or one of the options in the table that addresses the patient's comorbidities.

THE CARLAT REPORT
PSYCHIATRY
P.O. Box 626
Newburyport, MA 01950

This Issue:
Depression
January 2024

Next Issue:
Bipolar Disorder
February 2024

Your subscription expires:

Renew or extend online at
www.thecarlatreport.com
or by check using the order form below.

Expert Interview
Continued from page 4

one, we talked about how their half-lives and drug interactions differ, and really those are the main things that distinguish them. Paroxetine and fluoxetine are notorious for blocking the 2D6 system. That means they are going to double or triple levels of tricyclics, which can cause fatal cardiac arrhythmias. They also raise some antipsychotics (aripiprazole, brexpiprazole, iloperidone, and risperidone), which can cause akathisia and—over the long term—tardive dyskinesia. Fluvoxamine is not a 2D6 inhibitor but does raise a lot of drug levels by inhibiting other enzymes (1A2, 2C19, 3A4, and 3A5), and it has another notch against it because it is not FDA approved for the treatment of depression, only for OCD.

TCPR: Do some antidepressants have more of a dose-dependent response?

Dr. Schwartz: For the SSRIs, most of the evidence suggests there is not a clear dose-response curve. For the SNRIs, it's not as clear, but my experience suggests they work better as the dose goes up, and some evidence points that way as well. Vortioxetine may also have a dose-dependent response. The limitation here is that most studies are not large enough to detect differences between doses.

TCPR: Thank you for your time, Dr. Schwartz.

To learn more and earn additional CMEs, search for "Carlat" in your favorite podcast store and subscribe to our weekly podcast.